Investigating New Approaches: RNAi

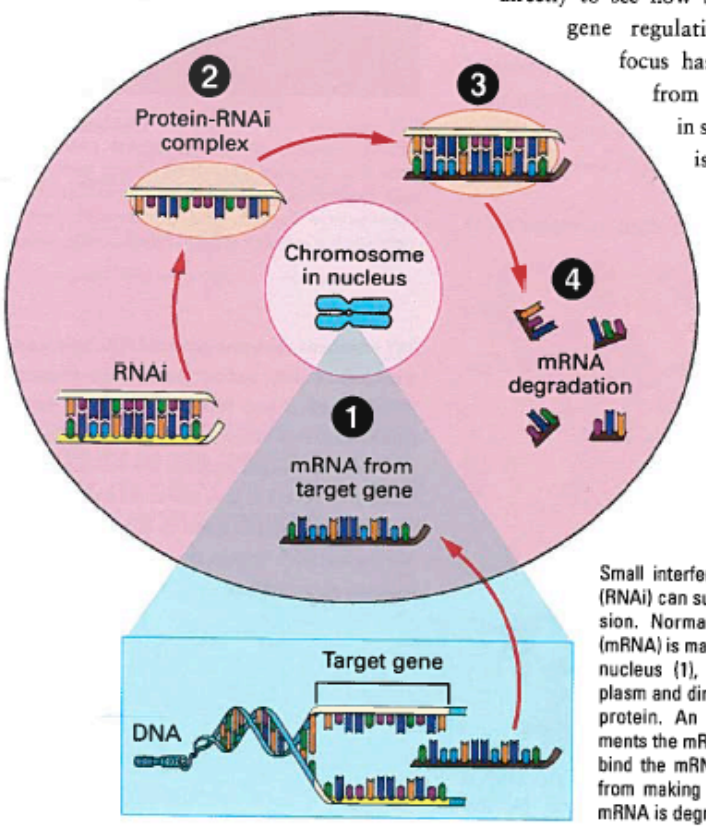
Thousands of genes can be studied simultaneously using RNA interference

RNAi IS BEING USED TO:

- identify and validate new anticancer targets
- delineate pathways involved in cancer and related processes
- run high-throughput screens for drug discovery
- explore mechanisms of action of drugs
- generate new cell and animal models

Thousands of genes can be studied simultaneously using RNA interference (RNAi) a powerful technique to silence gene expression. With RNAi technology, experiments that once took months or years are now performed in days or weeks. From an evolutionary perspective, this new technology exploits a cellular defense mechanism that recognizes and degrades the RNA of invaders such as viruses.

In addition to using RNAi technology as a tool to understand the regulation of gene expression and DNA repair, CCR researchers also explore cellular small RNAs directly to see how they contribute to gene regulation. CCR's dual focus has evolved directly from basic explorations in single-celled organisms. A few years ago, CCR's Dr. Susan Gottesman was exploring Escherichia coli bacteria as a model to develop methods to detect and characterize the function of small RNAs in gene regulation. She discovered the important ability of these small molecules to interact with specific protein-encoding RNAs and alter their regulation during stress responses and normal cellular metabolism.



Small interfering ribonucleic acid (RNAi) can suppress gene expression. Normally messenger RNA (mRNA) is made from a gene in the nucleus (1), moves to the cytoplasm and directs the building of a protein. An RNAi that complements the mRNA sequence (2) can bind the mRNA (3) and prevent it from making protein. Instead, the mRNA is degraded (4).

Extending the findings of Dr. Gottesman and others, Dr. Shiv Grewal, who joined CCR in 2003, showed that short interfering RNAs seem to be equally critical regulatory molecules in the more complex cells of animals and plants. As a researcher at Cold Spring Harbor Laboratories, Dr. Grewal unveiled the role of RNAi in shepherding certain types of chromosomal complexes, called heterochromatin, to their correct places in the nucleus. His research achievement was selected as "Breakthrough of the Year 2002" by Science magazine. The link between RNAi and chromatin assembly has broad implications for genome organization and structure in organisms as distantly related as the fruit fly and humans.

RNAi technology has become a popular research tool because it allows scientists to discover the molecular effects of modulating expression at the level of individual genes or at the level of a gene cluster, but RNAi and the related small RNAs play equally important roles in vivo as molecular gene regulators.

CCR is making a significant investment in RNAi technology, to speed access, validation, and application of RNAi technologies from their present role as research tools to a possible future use in cancer therapy.